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Pegfilgrastim Administered Once Per Cycle Reduces Incidence of Chemotherapy-Induced Neutropenia

Jeffrey Crawford

Duke Medical Center, Durham, North Carolina, USA

Abstract

Neutropenia is a common and potentially dangerous adverse effect of cancer chemotherapy. It also often necessitates a reduction or delay in dose, thus compromising efficacy. The human granulocyte colony-stimulating factor filgrastim has been proven to have a good safety profile and to be effective in accelerating neutrophil recovery and reducing the incidence of infections following myelosuppressive chemotherapy. However, its short serum half-life necessitates daily administration. Pegylated filgrastim (pegfilgrastim) was developed by attaching a polyethylene glycol moiety to the filgrastim protein. Pegfilgrastim binds to the same cell surface receptor on neutrophils and their precursors as filgrastim and stimulates the proliferation and differentiation of neutrophils through the same mechanism. However, because of the pegylation, it is minimally cleared by the kidneys and has a much longer serum half-life. Furthermore, its clearance is neutrophil dependent and thus 'self-regulated'. Pegfilgrastim is administered as a single subcutaneous injection per cycle of chemotherapy. In clinical trials it has been shown to be comparable in efficacy to filgrastim in decreasing the incidence of infection as manifested by febrile neutropenia following chemotherapy. Its safety profile and tolerability are similar to those of filgrastim.

1. Introduction

Adverse effects often necessitate a reduction or delay in dose of cancer chemotherapy. One of the most common, and potentially the most serious, adverse effects of chemotherapy is neutropenia. Febrile neutropenia (FN) can result in hospitalisation, infectious complications and death.[1,2] Since adherence to the scheduled chemotherapy regimen is closely related to clinical outcome, significant deviations from the planned dosage should be avoided.[3-5]

The human granulocyte colony-stimulating factor (G-CSF) filgrastim was approved for use in 1991 and has been proved effective in accelerating neutrophil recovery and reducing the incidence of infections following myelosuppressive chemotherapy. Filgrastim has been shown to have a good safety profile and to be effective in a wide variety of cancers, chemotherapy regimens and clinical settings, including congenital neutropenias. However, its relatively short serum half-life of approximately 3.5 hours necessitates daily administration by subcutaneous injection.

Pegylated filgrastim (pegfilgrastim) was created by attaching a polyethylene glycol (PEG) molecule to the filgrastim protein, specifically at the N-terminal methionine residue. The addition of the PEG molecule greatly increases the hydrodynamic size of the molecular complex, reduces excretion via the kidneys, and leaves neutrophil-mediated clearance as the apparent predominant route of excretion from the body.[6] The clearance of pegfilgrastim is therefore directly related to the absolute neutrophil count (ANC). During neutropenia, the serum concentration of pegfilgrastim remains elevated. As the ANC rises, the serum concentration decreases as the drug is cleared by the neutrophils. Because clearance is related to the individual patient's unique haematopoietic recovery, pegfilgrastim is considered to have patient-specific pharmacokinetics. The reduced frequency of dose administration reduces compliance concerns, simplifies management of chemotherapy-induced neutropenia, improves patient comfort (fewer injections), and may improve quality of life.

In clinical trials, pegfilgrastim has shown safety and efficacy comparable to that of an average of 11 daily injections of filgrastim in decreasing the incidence of infection as manifested by FN following chemotherapy. This article reviews the properties of and clinical experience with pegfilgrastim.

2. Pharmacology of Pegfilgrastim

2.1 Physiochemical Properties

Filgrastim is a 175-amino acid protein (recombinant human G-CSF) identical in amino acid sequence to endogenous G-CSF except for the addition of an N-terminal methionine. Unlike the native protein, filgrastim is nonglycosylated; it has a molecular weight of 18 800D. Pegfilgrastim is created by covalently binding a 20kD PEG molecule to filgrastim (figure 1). Pegfilgrastim has a molecular weight of 39 000D. Like filgrastim, pegfilgrastim acts by binding to specific surface receptors on haematopoietic cells to stimulate the proliferation and differentiation of neutrophil precursors as well as to enhance the end-cell functional activity, including phagocytosis, respiratory burst and antibody-dependent cytotoxicity.

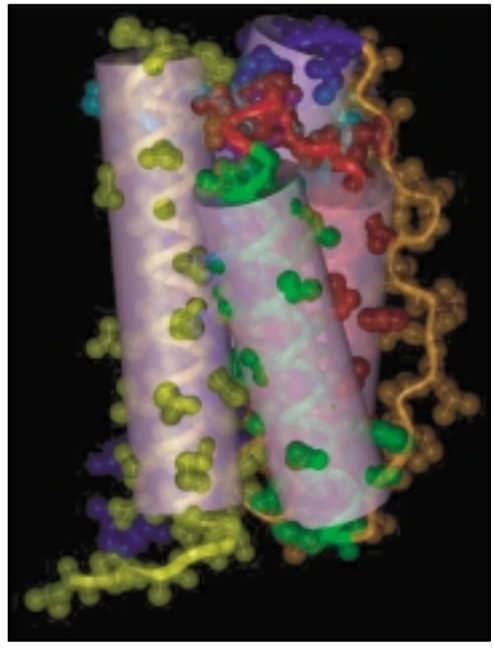

Fig. 1. Pegylated filgrastim (pegfilgrastim) molecule. (Image provided by Dr Osslund, Amgen, Department of Molecular Structure and Design. Pegfilgrastim Copyright 2002. All rights reserved, Amgen Inc.)

PEG is a nontoxic, nonimmunogenic, physiologically inert, water-soluble polymer that has been used extensively to modify proteins in order to lengthen their serum half-life and ultimately improve their pharmacological profile over that of the unmodified protein.[7] The size of the pegfilgrastim molecule is sufficient to minimise renal clearance, thus altering the pharmacokinetics such that neutrophil-mediated clearance appears to be the predominant method of elimination.[6,8] This self-regulating clearance mechanism makes it possible for the serum concentrations of pegfilgrastim to remain elevated during chemotherapy-induced neutropenia and then decline as the ANC recovers.

2.2 Mechanism of Action

Chemotherapy produces neutropenia by indiscriminately killing rapidly growing cells, which in-

clude not only cancer cells but myeloid precursor cells and neutrophils. Filgrastim and pegfilgrastim are recombinant human G-CSFs that act by binding to specific surface receptors on haematopoietic cell surfaces to stimulate the proliferation and differentiation of neutrophil precursors, as well as to enhance the end-cell functional activity, including phagocytosis, respiratory burst and antibody-dependent cytotoxicity. Repeated doses of filgrastim accelerate the transit of cells through the mitotic and the postmitotic stages.[9] Quantitative studies using radioisotopes have shown that the transit through the postmitotic compartment can be decreased by about 50%, from about 6 to 3 days; neutrophils therefore mature more quickly and are available to enter the bloodstream and fight infections sooner. Accompanying this response is a slight increase in the circulating half-life of the blood neutrophils. The increase in the blood neutrophil count is thus due to greater production and longer cell survival.[10] The neutrophils in patients treated with filgrastim following chemotherapy have been shown to have normal to enhanced function. Filgrastim tends to maintain or enhance the micro-organism–killing function of neutrophils. The net effect of filgrastim is identical to the natural response that is driven by endogenous G-CSF. However, endogenous G-CSF levels are generally not elevated in the absence of neutropenia and infection. The use of filgrastim after chemotherapy provides a 'proactive' approach to accelerating neutrophil recovery.

Patients treated prophylactically with filgrastim for chemotherapy-induced neutropenia experienced a statistically significant reduction in the incidence of infection and a 50% reduction in the duration of severe neutropenia (ANC <500/μl), in the first cycle of chemotherapy from approximately 6 to 3 days.[11,12] The magnitude of this effect was very similar to the shortening of neutrophil recovery time seen in studies in healthy volunteers. These findings suggest that the principal effects of filgrastim are to promote the proliferation and survival of precursor cells and differentiation into neutrophils. Clinically, the decreased duration of severe neutropenia results in reductions in both hospitalisation rate and the number of days of intravenous antibiotic use.[11,12] Pegylation does not alter these biological activities of filgrastim.[13,14] Proliferation assays found a similar stimulation of G-CSF–dependent cells by pegfilgrastim and filgrastim. Stimulation of granulocytopoiesis and neutrophil kinetics is also similar.[15] Pegfilgrastim and filgrastim have similar competitive binding affinity for G-CSF receptors on neutrophils. Their neutrophil dose-response is similar in terms of number of cells and neutrophil function.

2.3 Pharmacokinetics

The pharmacokinetics of pegfilgrastim have been studied after single and repeated subcutaneous doses in adult patients with cancer (table I) and in healthy volunteers (figure 2).[6,8,16]

In healthy adult volunteers, single subcutaneous pegfilgrastim doses ranging from 30 to 300 μg/kg were generally well tolerated and produced increases in the ANC and circulating CD34+ cell counts.[6] The neutrophil counts increased from the pretreatment values in a dose- and time-dependent fashion, to median values of 30.4×10^9 cells/L and 50.8×10^9 cells/L in the lowest- and highest-dose cohorts, respectively.[6] The median duration of response was 5.79 days in the 30 μg/kg group and was more than 8 days in the other groups (60, 100 and 300 μg/kg).

Unlike filgrastim, which has predominantly dose-linear elimination (mainly by renal excretion), pegfilgrastim has self-regulated and saturable neutrophil-mediated elimination. After a single subcutaneous dose of pegfilgrastim, the peak se-

Table I. Pharmacokinetic profile (median values) of a single dose of pegfilgrastim (100 μg/kg) in adult patients with lung cancer (n = 3)[8]

Peak plasma concentration (μg/L)	114
Time to peak concentration (h)	72
Half-life (h)	33.2
Area under the concentration-time curve (ng • h/ml)	7150
Clearance (ml/h/kg)	14.0

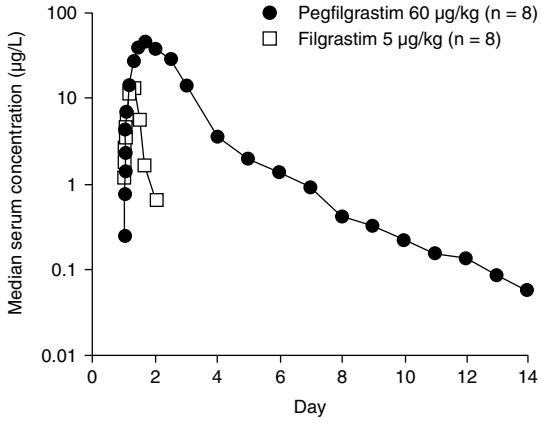

Fig. 2. Pegfilgrastim serum concentrations after administration to healthy volunteers.

rum concentration occurred between 24 and 72 hours after administration, and serum concentrations were maintained during the period of neutropenia following myelosuppressive chemotherapy.[8] The distribution of pegfilgrastim was limited to the plasma compartment. In patients with non–small-cell lung cancer who were given subcutaneous doses of 30, 100 or 300 µg/kg, elimination was nonlinear with respect to the dose. Serum clearance decreased with increasing dose, indicating a saturated clearance mechanism. This phenomenon was attributed to the important role that the binding of pegfilgrastim to neutrophils and neutrophil precursors plays in elimination.[8]

Similarly, a reduced myeloid mass prolongs the elimination of pegfilgrastim. In this same study, the same doses of pegfilgrastim were administered to patients 14 days before the first cycle of chemotherapy and again 24 hours after the completion of the chemotherapy.[8] Peak serum concentrations were similar with each dose, whether given before or after the chemotherapy. However, the rate of clearance was lower for the dose given after chemotherapy, when the myeloid mass was reduced, than when pegfilgrastim was administered before chemotherapy, while the white blood cell count was within the normal range (figure 3). At the onset of haematological recovery, the serum concentration of pegfilgrastim decreases because of receptor-mediated clearance by neutrophils (figure 4). This ANC-dependent clearance protects patients during their recovery from the effects of myelosuppressive chemotherapy without compromising subsequent cycles of chemotherapy.

The pharmacokinetics of pegfilgrastim in the geriatric population (≥65 years) were similar to those in younger adults. No sex-related differences in pharmacokinetics have been observed. Pharmacokinetic studies have not been conducted in paediatric patients.

The pharmacokinetics of pegfilgrastim have not been studied in patients with renal impairment. However, renal clearance of pegfilgrastim is negligible. Animal studies showed that the plasma clearance of pegfilgrastim was similar in bilaterally nephrectomised rats and rats with normal renal function.

No studies have been conducted in patients with hepatic failure. However, the pharmacokinetics of

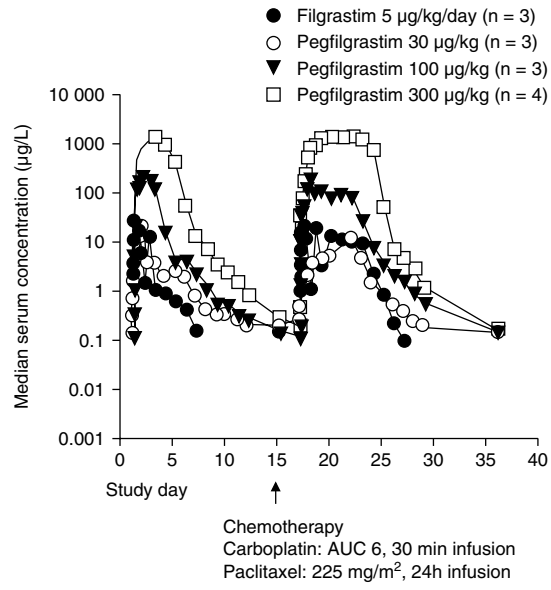

Fig. 3. Serum pegfilgrastim concentration after chemotherapy. Area under the concentration-time curve (AUC) = 6 mg/ml. (Reproduced from Johnston E, Crawford J, Blackwell S, et al. Randomized, dose-escalation study of SD/01 compared with daily filgrastim in patients receiving chemotherapy. J Clin Oncol 2000; 18: 2522-8.[8] 2000 Lippincott Williams & Wilkins©.)

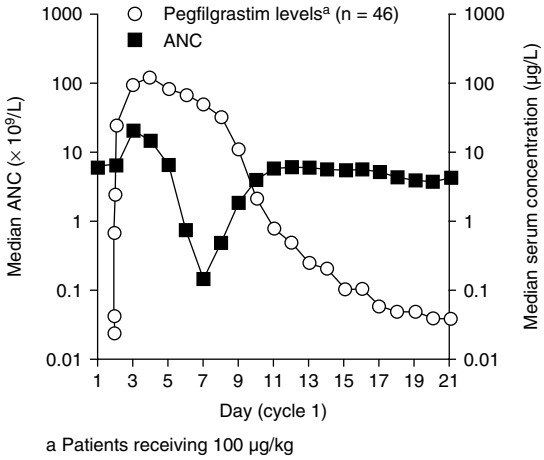

Fig. 4. Pegfilgrastim serum concentrations in relation to the absolute neutrophil count (ANC) nadir and ANC recovery.

pegfilgrastim are not expected to be affected by hepatic impairment, given its novel neutrophil-dependent elimination mechanism.

2.4 Pharmacodynamics

Pegfilgrastim produces a dose-dependent increase in neutrophil counts. The ANC rises rapidly after its administration, and the duration of the response is more sustained than after daily injections of filgrastim.[6,8] Furthermore, the postnadir ANC levels return to the pretreatment value, and pegfilgrastim concentrations return to normal. As a result, there is minimal 'overshoot' of the ANC, as is observed occasionally with the recommended daily course of filgrastim during postnadir neutrophil recovery.[17-19]

2.5 Preclinical Toxicology

Pegfilgrastim has biochemical activity similar to that of filgrastim, which is negative in the standard Ames mutagenesis assay. Given the chemical nature of the attached PEG moiety and the similarity of pegfilgrastim to filgrastim, it is unlikely that pegfilgrastim would be carcinogenic when used as directed. The preclinical toxicology of pegfilgrastim has been studied *in vivo* in animals.[20] No specific carcinogenesis testing has been conducted with pegfilgrastim, but long-term administration did not cause the development of precancerous or cancerous lesions in rats that were given pegfilgrastim as weekly subcutaneous injections of up to 1000 μg/kg for 6 months.

Pegfilgrastim did not adversely affect any indices of mating or fertility in rats that were given weekly subcutaneous injections of up to 1000 μg/kg for 2 to 4 weeks before mating. Well-controlled studies of pegfilgrastim in pregnant women have not been done. However, animal data suggest that very low levels of pegfilgrastim cross the placenta, and pegfilgrastim has been shown to have adverse effects in pregnant rabbits when it was given every other day at doses as low as 50 μg/kg. Pregnant rabbits experienced decreased food consumption and/or weight gain at pegfilgrastim doses of 50 to 1000 μg/kg administered every other day. Decreased fetal weight was also seen. At doses of 200 to 1000 μg/kg every other day, there were increased postimplantation losses and a decreased number of live births. No visceral or skeletal malformations were seen in rabbit fetuses at doses up to 200 μg/kg every other day. External malformations were not seen in rabbit fetuses at doses up to 1000 μg/kg every other day.

No external, visceral or skeletal malformations were seen in the fetuses when pegfilgrastim was administered to pregnant rats at doses up to 1000 μg/kg every other day. There was an increased incidence of bent or wavy ribs, a reversible pathological finding. No maternal or neonatal toxicities were seen in rats given once-weekly subcutaneous injections of pegfilgrastim at doses up to 1000 μg/kg in a prenatal and postnatal development study.

3. Clinical Trials of Pegfilgrastim

3.1 Efficacy

Pegfilgrastim has been evaluated in phase I and II trials in patients with breast cancer, lung cancer, non-Hodgkin's lymphoma and Hodgkin's disease, and in phase III trials in breast cancer

patients.[8,18,19,21,22] Dose-ranging studies found that doses ranging from 30 to 300 μg/kg were generally well tolerated.[8,17] Both the 60 and the 100 μg/kg doses of pegfilgrastim elicited a neutrophil response similar to that with filgrastim, but the average duration of severe neutropenia and the percentage of patients with 3 or more days of severe neutropenia was lowest in the pegfilgrastim 100 μg/kg group. Furthermore, the average ANC nadir was highest in this group. The 100 μg/kg dose of pegfilgrastim was therefore chosen for a phase III study. To simplify the administration of pegfilgrastim, one of the pivotal trials evaluated a 6mg fixed dose of pegfilgrastim in comparison with daily subcutaneous injections of filgrastim. The 6mg dose was chosen on the basis of pharmacokinetic and pharmacodynamic modelling and evidence of efficacy obtained from the phase II dose-ranging study and analysis of the findings in breast cancer patients.[23] Further analysis revealed that patients who were given at least 6mg of pegfilgrastim had a duration of severe neutropenia less than the duration in patients who were given only 4mg. A 6mg fixed dose ensures an effective, equivalent weight-based dose in patients at both ends of a wide spectrum. Given the ability of a 6mg fixed dose to accommodate the majority of patients who are likely to be seen in clinical practice, a pivotal trial was designed to further confirm the safety and efficacy of this fixed dose compared with those of daily injections of filgrastim.

A single dose of pegfilgrastim given once per chemotherapy cycle was as effective as daily injections of filgrastim with respect to neutropenia-related endpoints in two large, randomised, blinded, controlled clinical trials.[18,19] Both trials were conducted in women with breast cancer who were treated with doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 every 3 weeks for up to 4 cycles. In one trial the patients were given pegfilgrastim 100 μg/kg 24 hours after the chemotherapy, followed by daily placebo; in the other trial they were given a 6mg fixed dose of pegfilgrastim 24 hours after chemotherapy, followed by daily placebo. Both trials used filgrastim 5 μg/kg/day, beginning 24 hours after chemotherapy, as the active comparator. The duration of severe neutropenia in one cycle, defined as an ANC <500/μl, was the primary endpoint in both studies. After chemotherapy, patients treated with either pegfilgrastim or filgrastim had a peak in median ANC at day 3, with the ANC nadir occurring on day 7. In the recovery phase after the nadir, the ANC exceeded the pretreatment value in patients given filgrastim, but the postrecovery ANC in patients given pegfilgrastim levelled off at around the pretreatment values (figure 5). Furthermore, consistent with its self-regulating pharmacokinetics, the serum levels of pegfilgrastim remained elevated throughout the nadir, but began to decline during neutrophil recovery. In both studies, pegfilgrastim was found to be equivalent to filgrastim with respect to duration of severe neutropenia in cycle 1 and across all cycles. Furthermore, in the fixed-dose study, there were no differences in the duration of severe neutropenia between treatment groups when analysed by pretreatment bodyweight (table II). The ANC recovered in all patients treated with pegfilgrastim or filgrastim.

The incidence of FN (defined as an oral-equivalent temperature ≥38.2°C during an ANC <500/μl) in patients treated with pegfilgrastim was lower than in those treated with filgrastim in each study (table III). Most patients with FN experienced the event in cycle 1, and the majority of patients who were treated with four cycles of chemotherapy remained event-free throughout all four cycles.[18,19] In the weight-based–dosage study, the incidence of FN over all cycles of chemotherapy was significantly lower in patients given pegfilgrastim than in those given filgrastim ($p = 0.029$). The incidence and duration of grade 4 neutropenia were less in the pegfilgrastim group over all cycles (table IV).[18] Data from the fixed-dose study show a similar trend, but the difference in the incidence of FN did not reach statistical significance in this trial, possibly because of the smaller sample size. However, these studies were not designed to establish the superiority of pegfilgrastim for FN.

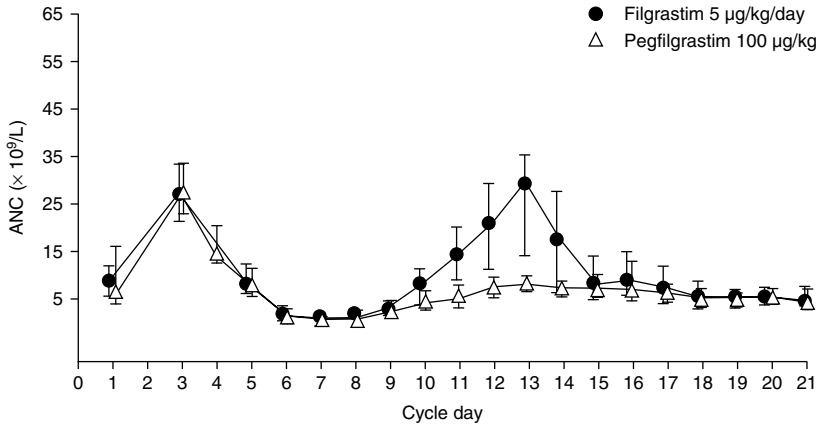

Fig. 5. Median absolute neutrophil count (ANC) levels after pegfilgrastim and filgrastim. (Reproduced from Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002; 20: 727-31.[18] 2002 Lippincott Williams & Wilkins©.)

In the weight-based–dosage study, 94% of the patients who received pegfilgrastim and 95% of those who received filgrastim were given full doses of chemotherapy on time (≥80% of the drug doses given in cycle 1, with the doses given no more than 3 days after the planned start of the subsequent cycle). In the fixed-dose study, the rates were 90% for pegfilgrastim and 89% for filgrastim.

The efficacy of a single 100 μg/kg dose of pegfilgrastim per chemotherapy cycle was similar across several types of chemotherapy regimens and cancers. Patients who were given lower doses of pegfilgrastim were more likely to have longer durations of severe neutropenia, with an increased subsequent risk for the development of FN.[8,16,17,22,25]

Table II. Mean duration of severe neutropenia in cycle 1, by bodyweight cohort[24]

Pretreatment weight (kg)	Duration of severe neutropenia (days)[a]	
	pegfilgrastim (6mg fixed dose)	filgrastim (5 μg/kg/day)
≤62	1.6	1.8
63 to ≤71	2.3	1.6
72 to ≤80	1.7	1.2
>80	1.7	1.2

a All differences between treatment cohorts are not significant.

3.2 Safety and Tolerability

The safety and tolerability of pegfilgrastim have been evaluated in over 500 individuals, including 465 cancer patients given several doses in conjunction with multiple cycles of chemotherapy.[8,17-19,21] The safety and tolerability profiles of pegfilgrastim and filgrastim were comparable with respect to changes in laboratory values and the incidence and types of adverse events. In clinical trials involving patients with breast cancer, lung cancer or lymphoma given pegfilgrastim after cytotoxic chemotherapy, most adverse events were the sequelae of the underlying malignancy or chemotherapy. In all phase II and III trials, medullary bone pain, reported in 26% of patients, was the only consistently observed adverse reaction attributed to pegfilgrastim. This bone pain was generally reported to be of mild-to-moderate severity and could be controlled in most patients with non-narcotic analgesics; infrequently, bone pain was severe enough to require narcotic analgesics. No patients withdrew from any trial secondary to bone pain.

Serious treatment-related adverse events were reported in 4% of the patients who were given pegfilgrastim and in 7% of the patients who were

Table III. Incidence of febrile neutropenia by treatment and cycle (Reproduced from Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002; 20: 727-31.[18] 2002 Lippincott Williams & Wilkins©.)

Cycle	Filgrastim (n = 147)	Pegfilgrastim (n = 1490)	Difference in 95% CL	95% CL	p value
1	18 (12%)	11 (7%)	–4.9	–11.7, 1.9	0.174
1 to 4	27 (18%)	14 (9%)	–9	–16.8, –1.1	0.029

CL = confidence limit.

given filgrastim. Thirty-two patients (7%) who received pegfilgrastim and 22 patients (7%) who received filgrastim withdrew from the studies because of adverse events that were reported to be related to the study drug. Thirteen deaths within 30 days after study drug administration were reported, six in patients given pegfilgrastim and seven in those given filgrastim. All of the deaths were directly related to complications of the patients' underlying malignancy or its treatment. The only serious event that was not deemed attributable to underlying or concurrent disease or to concurrent therapy was a single case of hypoxia. Although not reported in patients receiving pegfilgrastim, rare events of adult respiratory distress syndrome, splenic rupture and sickle cell crisis have been reported in patients receiving the parent compound, filgrastim. Across all studies, no life-threatening or fatal adverse events were attributable to pegfilgrastim.

Clinical laboratory parameters of patients given pegfilgrastim were consistent with those expected in patients given filgrastim. Mild-to-moderate elevations in lactate dehydrogenase, uric acid and alkaline phosphatase levels occurred in both treatment groups and were reversible. There were no differences between study groups in haemoglobin levels or platelet counts at the end of treatment. Neutralising antibodies were not detected in any patient treated with pegfilgrastim or filgrastim. No differences in tolerability or safety were noted in subcategories of patients on the basis of bodyweight, sex or age, including age >65 years.

4. Clinical Use

A single dose of pegfilgrastim per cycle of chemotherapy is indicated to decrease the incidence of infection as manifested by FN in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs. The recommended dose is 6mg administered by subcutaneous injection. Pegfilgrastim should be administered approximately 24 hours after the administration of cytotoxic chemotherapy and continued in all subsequent cycles. In clinical studies, pegfilgrastim has been administered 14 days before the next cycle of chemotherapy with an acceptable safety profile.

In theory, because pegfilgrastim stimulates the proliferation of neutrophil precursors at the time of exposure to cytotoxic chemotherapy, it could have the unintended effect of worsening neutropenia if administered concurrently with chemotherapy. Until studies are performed to document the safety of concurrent administration, it is recommended that pegfilgrastim be administered approximately

Table IV. Incidence of grade 4 neutropenia[a] by cycle and treatment group (Reproduced from Holmes FA, O'Shaughnessy JA, Vukelja S, et al. Blinded, randomized, multicenter study to evaluate single administration pegfilgrastim once per cycle versus daily filgrastim as an adjunct to chemotherapy in patients with high-risk stage II or stage III/IV breast cancer. J Clin Oncol 2002; 20: 727-31.[18] 2002 Lippincott Williams & Wilkins©.)

Cycle	Incidence (% patients)			Mean duration (days)		
	filgrastim	pegfilgrastim	p value	filgrastim	pegfilgrastim	p value
1	79	77	>0.500	1.8	1.7	>0.500
2	56	45	0.058	1.1	0.7	0.001
3	60	37	<0.001	1.2	0.6	<0.001
4	55	45	0.094	1.3	0.9	<0.025

a Absolute neutrophil count <900/μl.

24 hours after the administration of chemotherapy. Pegfilgrastim is a growth factor that stimulates primarily neutrophils and neutrophil precursors. However, the G-CSF receptor, through which pegfilgrastim and filgrastim act, has been found on some tumour cell lines, including myeloid and T-lymphoid leukaemia, lung, head and neck, and bladder cancers. *In vitro* proliferation has been observed in response to filgrastim in some of these cell lines, particularly acute myeloid leukaemia lines. Although no such stimulation has been reported to be clinically relevant, the possibility that pegfilgrastim can act as a growth factor for certain tumours cannot be excluded.

Pegfilgrastim is contraindicated in patients with known hypersensitivity to *Escherichia coli*-derived proteins, filgrastim, pegfilgrastim or any other components of the product.

A white blood cell count $>100 \times 10^9$/L developed in fewer than 1% of the patients with cancer in the clinical trials of pegfilgrastim. The development of leucocytosis was not associated with any reported adverse clinical effects. In general, peak white blood cell counts after haematological recovery from chemotherapy-induced neutropenia are lower with pegfilgrastim than with filgrastim, because of receptor-mediated clearance of the pegfilgrastim. It is important after the administration of chemotherapy to monitor a patient's haematological status with a complete blood cell count and platelet count (twice weekly), particularly during the first cycle of treatment. For all subsequent cycles, patients should have adequate counts before chemotherapy is administered, since myelosuppression is often a consequence of such therapy.

Drug interactions between pegfilgrastim and other drugs have not been fully evaluated. Theoretically, a pharmacodynamic, synergistic interaction could occur with other drugs that stimulate the release of neutrophils, such as lithium-containing drugs. These drugs should be used with caution during treatment with pegfilgrastim.

Pegfilgrastim is classified as Pregnancy Category C and should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus; there are no adequate and well controlled studies in pregnant women. Pegfilgrastim has been shown to have adverse effects in pregnant rabbits when given every other day at doses as low as 50 μg/kg.

No differences in efficacy or safety due to age have been observed. More than 20% of the patients given pegfilgrastim in the clinical trials were aged ≥65 years. The safety and efficacy of pegfilgrastim in paediatric patients have not yet been established.

5. Conclusions

Pegfilgrastim, which is produced by adding a PEG molecule to the N-terminal of the filgrastim protein, binds to the same cell-surface receptor on neutrophils and their precursors as filgrastim. It thus stimulates the proliferation and differentiation of neutrophils through the same mechanism. However, since pegfilgrastim undergoes minimal renal clearance, it appears that its elimination is neutrophil mediated. Serum concentrations remain elevated during a neutropenic episode. As the ANC rises, the serum concentration decreases as the drug is cleared by the neutrophils.

Pegfilgrastim has been shown to be comparable to filgrastim in reducing the duration of severe neutropenia, reducing the incidence of FN, and promoting neutrophil recovery in patients given myelosuppressive chemotherapy. The recommended dose is a single 6mg fixed dose per cycle, given subcutaneously 24 hours after chemotherapy. This dose has been shown to have a good safety profile and to be effective, regardless of pretreatment bodyweight (range 46 to 125kg), in a phase III clinical trial.

Pegfilgrastim is generally well tolerated. The adverse events reported were mainly those due to the underlying malignancy or to chemotherapy. Mild to moderate medullary bone pain was the only consistently reported adverse event associated with filgrastim or pegfilgrastim in clinical trials.

Neutropenic complications are a serious risk in all patients treated with myelosuppressive chemo-

therapy. Neutropenia also often leads to a reduction or delay in dosage, which may result in compromised treatment efficacy. Reducing the risk of neutropenia and its complications, such as infection, hospitalisation and possibly death, requires proactive management. Pegfilgrastim builds on the established benefits of filgrastim, providing equal protection with a simplified dosage regimen that may improve compliance and enhance quality of life in patients treated with myelosuppressive chemotherapy.

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Correspondence and offprints: *Jeffrey Crawford*, Duke Medical Center, Room 25178 Morris Bldg., PO Box 3198, Durham, NC 27710-0001, USA.
E-mail: crawf006@mc.duke.edu